ARTICLES

Residential Radon Exposure and Lung Cancer Among Nonsmoking Women

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Background: **Radon at sufficiently high concentrations is known to cause lung cancer among underground miners and in experimental laboratory animals.** ***Purpose:*** **Our aim was to determine whether indoor levels of radon are associated with a detectable increase in lung cancer. Nonsmoking women were selected because they offer the best opportunity to detect radon-related risk while minimizing the potentially confounding influences of cigarette smoking and occupation.** ***Methods:*** **A population-based, case-control study of incident lung cancer was conducted in Missouri. A total of 538 nonsmoking white women diagnosed with lung cancer between 1986 and 1992 and 1183 age-matched control subjects were identified from the Missouri Cancer Registry and from driver's license and Medicare listings, respectively. Information on lung cancer risk factors was obtained by telephone interview. Year-long radon measurements were sought in every dwelling occupied for the previous 5-30 years.** ***Results:*** **Radon measurements covered 78% of the relevant residential period, and women reported being indoors for 84% of this time. The time-weighted average radon concentrations were exactly the same for case subjects and control subjects (1.82 pCi/L of air [pCi L^{-1}]). Radon levels greater than 4 pCi L^{-1} were experienced by 6.5% of the case subjects and 6.8% of the control subjects. For all data combined, there was little evidence for a trend of lung cancer with increasing radon concentrations (two-tailed trend test, *P* = .99 continuous data analysis; *P* = .19 categorical data analysis).** A **positive dose-response trend was suggested for the adenocarcinoma cell type and among directly interviewed women (two-tailed trend test; *P* = .31 continuous data analysis; *P* = .04 categorical data analysis), but not for other histologies or among those who had surrogate interviews.** ***Conclusions:*** **The possibility of detecting a risk from indoor radon in this study was maximized by *(a)* including a large number of nonsmoking women with high indoor occupancy, *(b)* conducting a large number of radon measurements near the time of the diagnosis of cancer, and *(c)* controlling for known causes of lung cancer. However, an association between lung cancer and the exposure to domestic levels of radon was not convincingly demonstrated.** ***Implications:*** **The magnitude of the lung cancer risk from radon levels commonly found in U.S. dwellings appears low. [J Natl Cancer Inst 86:1829-1837, 1994]**

Epidemiologic studies *(1-3)* of underground miners and experimental studies of laboratory animals leave little doubt that high levels of exposure to radon and radon's decay products (^{218}-polonium, ^{214}-polonium) can increase the risk of lung cancer. Applying risk estimates based on underground miner studies to residential environments has been questioned, however, because of the substantial differences between an aboveground home and an underground mine, including the possible confounding or enhancing influence of such mine exposures as silica, arsenic, diesel exhaust, and blasting fumes *(4)*. Demonstrating that typical residential levels of radon cause lung cancer has also been a formidable undertaking. There are inherent difficulties in estimating accurately radon exposures that occurred many years in the past, as well as methodologic difficulties in detecting small increases in lung cancer risk amidst a number of potential confounding factors. Clarifying the level of risk from residential exposures is of major public health importance because radon is ubiquitous in the earth's crust and might be responsible for thousands of lung cancer deaths nationally *(5,6)* and throughout the world.

Stidley and Samet *(7)* have reviewed at least 15 descriptive or ecologic surveys that have attempted to correlate estimates of regional radon exposure with rates of lung cancer. The limitations of these studies are so severe (e.g., the absence of individual exposure estimates and the inability to control for cigarette smoking), that they are essentially noninformative for estimating radon risks *(7)*. Six case-control studies that

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See "Notes" section following "References."

measured current radon concentration levels in present and, in some cases, former homes also have been conducted in Shenyang, China *(8);* the state of New Jersey in the United States *(9);* Stockholm *(10)* and all other Swedish regions in the national Swedish study *(11);* Finland *(12);* and Manitoba, Canada *(13).* The results of these studies are inconsistent. No link between lung cancer and indoor radon was found in China, Finland, and Canada. Slight increases were suggested in New Jersey and Stockholm. A strong correlation was reported in the national Swedish study. A combined analysis *(14)* of the China, Stockholm, and New Jersey studies revealed no evidence of a radon-related risk, despite nearly 1000 lung cancer cases available for analysis.

To extend the quantitative assessment of lung cancer risk associated with residential radon exposure, we conducted a population-based case-control study of women in Missouri who were either lifetime nonsmokers or former smokers who quit 15 or more years ago. Nonsmoking women were selected because they offer the best opportunity to detect radon-related risks while minimizing the potentially confounding influences of cigarette smoking and occupation.

Subjects and Methods

Both lifetime nonsmokers and former smokers were included in the study. Lifetime nonsmokers were defined as women who did not smoke more than 100 cigarettes or use any other tobacco products for more than 6 months. Former smokers were defined as women who ceased using all tobacco products 15 or more years prior to interview (the median period of smoking cessation was 24 years).

Case Subjects

Case subjects were nonsmoking white women between 30 and 84 years of age with primary cancer of the lung reported to the Missouri Cancer Registry between June 1, 1986, and June 1, 1991. Selection was limited to white subjects because of the limited numbers of other racial and ethnic groups. Nonsmoking women could be selected from the Missouri Cancer Registry because the registry collects information on smoking history with high accuracy *(15).* The registry is estimated to capture 95% of cancer cases in Missouri. For the current study, additional case ascertainment was conducted to increase coverage to nearly 100%,

A total of 650 eligible case subjects were identified in this manner. A screener questionnaire was administered by telephone to determine and/or verify eligibility on age, sex, race, and smoking status. A comprehensive telephone interview was completed by 618 case patients (95%) between January I, 1988. and September 1, 1991, to assess demographic factors, occupational history, lifetime passive smoking, previous active smoking, previous nonmalignant lung disease. and usual diet. Year-long alpha-track measurements were made in the current and previous homes of 538 case patients (83%). Measurements were not obtained for 80 case subjects for the following reasons: the respondent (10 case subjects) or next-of-kin or landlord (11 case subjects) refused to participate in the study, or previous dwellings were out of state. destroyed, or were unable to be located (59 case subjects). Telephone interviews were obtained for 197 living case subjects**(37%).** Because 341 case subjects (63%) either had died or were too ill to participate in an in-person interview, interviews with next-of-kin were conducted.

In addition to the registry-reported diagnosis of lung cancer, tissue slides were reviewed for histologic verification for 409 (76%) of the case patients. Slides were examined simultaneously by three pathologists (T. Loy, J. Myers, and E. Ingram) using a multiheaded microscope and without knowledge of the referring pathologist's diagnoses. For surgical specimens, consensus diagnoses were based on the criteria outlined in the World Health Organization classification scheme *(16).* When only cytologic material was available, consensus diagnoses were based on standard cytologic criteria*(17).*

Control Subjects

A population-based sample of white, nonsmoking female control subjects was selected from two sources. For women between 30 and 64 years of age, names and addresses were randomly selected from driver's license files provided by the Missouri Department of Revenue. For women between the ages of 65 and 84 years, names and addresses were randomly selected from lists of Missouri women provided by the Health Care Financing Administration, which include an estimated 95% of women of this age *(18).* Driver's license files and Health Care Financing Administration files are updated annually. The number and age distribution of the control subjects selected for interview were frequency matched (in 5-year age strata) based on the number of case subjects reported to the registry in previous years. Most telephone numbers for case subjects and control subjects were obtained from a company that matched by computer names and addresses with telephone numbers. Telephone numbers not identified in this manner were sought by using directory assistance and local telephone directories and by contacting relatives. If a telephone number was still not found, a letter was mailed to the study subject requesting a telephone number for interview. By use of these methods, 1527 of 1587 nonsmoking control subjects responded to the initial screening inter-view; of these 1527 subjects, 1402 (92%) agreed to complete the full telephone interview and 1183 (78%) had year-long alpha-track measurements made in at least one home that they had occupied during the previous 5-30 years. Measurements were not obtained for 219 control subjects for the following reasons: The respondents (21 control subjects) or the next-of-kin or landlord (21 control subjects) refused to participate in the study, or previous dwellings were out of state, destroyed, or could not be located (177 control subjects).

Radon Measurements

Radon concentrations were measured in units of picocuries per liter of air (pCi L^{-1}). The Environmental Protection Agency (EPA) action level for home remediation is set at 4 pCi L^{-1}. Other countries have different recommendations, e.g.. 5 pCi L^{-1} in the United Kingdom and 10 PCi L^{-1} in Canada. One PCi L^{-1} is equivalent to 37 Bq m^{-3}. Radon measurements were made during the period from 1988 through 1992, which was as near as possible to the time of the diagnosis of cancer.

Current residential radon concentrations were measured by placing two alpha-track detectors (Terradex Corporation, Glenwood, Ill.) its each dwelling that had been occupied for at least 1 year by the study subject during the preceding 30 years in the state of Missouri. One detector was placed in the bedroom and the other in the kitchen for 12 months. A limited number of dwellings also had additional winter readings made every 3 months in the kitchen, bedroom, and basement to assess the degree of variation within homes and with each season. Placement was done by trained field technicians following a written protocol. Study personnel called each household 1 month after the field visit and sent reminder postcards to the participants in each household requesting that they check to ensure that the dosimeters were in place 3, 6, and 9 months after the initial visit. A label containing a toll-free telephone number was also placed in a convenient location in each dwelling for the respondent to call if any problems, with the detectors arose. Twelve months after placement of the detectors, each household was sent a container and requested to mail back the dosimeters to the study office in St. Louis, Mo, If dosimeters had been lost or misplaced, two new dosimeters were placed in the dwelling. After the detectors arrived in St. Louis, they were batched and mailed to the Terradex Corporation for analysis.

Three different quality control procedures were used to monitor radon assessment procedures. First, one blank (i.e., unexposed) dosimeter was shipped together with each batch of 20 dosimeters gathered from households in the study. This procedure determined radon exposure incurred during shipment and also validated the laboratory's ability to assess accurately detectors exposed to low-level alpha radiation.

The second procedure was to place a third detector in every 20th household. This detector was placed next to one of the other detectors left in the household. If the two side-by-side detectors did not agree within 20%, additional monitoring was attempted in that particular household. There was good agreement between the measurements of the two side-by-side detectors, and few households required additional measurements.

The third procedure was to periodically expose a sample of detectors to known levels of alpha radiation in radon chambers at the Geotech Corporation

(Grand Junction, Colo.). After exposure, these dosimeters were hatched with dosimeters from study households to monitor the accuracy of radon measures of 1.5, 2.5, 5.0, and 7.5 pCi L^{-1}. There was excellent concordance overall with the repeated measured values for the 149 blank and the 134 known standard exposures; the averages were 0, 1.4, 2.6, 5.1, and 7.6 pCi L^{-1}, respectively.

Radon measurements were made to estimate exposure conditions for the period 5-30 years prior to enrollment in the study. The 5-year interval was chosen because studies of underground miners indicate that a minimum latency period of about 5 years is necessary before radiogenic lung cancer would develop *(19,20).* The 30-year upper limit for the historical reconstruction of exposure was chosen because studies of miners indicate that risk decreases with time since exposure *(21)* and because estimates of prior radon exposures become increasingly inaccurate with time.

Time-weighted average (TWA) concentrations for this period were calculated. For subjects who had only one dwelling measured. the TWA exposure measure was the value ascribed to that home. When more than one dwelling was measured, the TWA exposure estimate was the mean radon concentration of all measured homes weighted by the years of residence spent in each home. Residential occupancy was obtained from questionnaire information to account for time spent outside the home (i.e., worktime and recreational time) during each time period of radon measurements. The average number of residences for both case patients and control subjects was 2.0 for the period 5-30 years prior to enrollment in the study. The mean residency time for case patients and control subjects in their most recent residences was 12.7 and 13.1 years, respectively.

Statistics

The measure of association between exposure to indoor radon and the development of lung cancer was the odds ratio (OR). The OR compares the odds of exposure to a specific radon concentration of case patients with that of control subjects. Multivariate logistic regression methods were used to compute ORs and their confidence intervals (CIs) and to adjust for potential confounding variables *(22).* Both TWA radon concentrations (pCi L^{-1}) and cumulative radon exposure measures (working-level-months [WLM]) were used to categorize radon exposure. To compute cumulative WLM, we set missing values for case subjects or control subjects equal to the mean radon concentration of the case or control distribution, respectively. An equilibrium ratio of 50% was assumed, and an occupancy factor, based on the interview data, of 84% was used. The cumulative WLM for the 5- to 30-year exposure period was approximately 10 WLM for both case patients and control subjects. Results of TWA concentration and WLM analyses were similar, and only the TWA radon exposure analysis is presented. Time-weighted average radon exposure was categorized into quintiles and deciles based on the distribution of values for controls. After stratification by potential confounding variables. the trend in ORs over radon concentrations was evaluated using a score test. which is equivalent to the Mantel extension test for linear trend *(22).* The test statistic is the same under a log-linear or a linear model. Analyses revealed that the *P* value for trend could vary considerably, depending on whether a continuous value or a mean value within exposure categories was used as the quantitative value. Continuous *P* values for trend are presented in the text. Both continuous and categorical-based two-sided *P* values for trend are presented in the tables. Consequences and implications for those differences are considered in the "Discussion" section.

Results

The mean age of women at lung cancer diagnosis was 71 years, and 46.3% were older than age 75. Little difference was found in either the marital status or education levels of the case patients and control subjects (Table 1). Most study subjects were either married or widowed, while a much smaller proportion were separated, divorced. or never married. Most women had completed at least 12 years of formal education.

Earlier analyses *(23-25)* revealed significant differences between case patients and control subjects in the proportion of former smokers, the frequency of pre-existing nonmalignant lung disease. the amount of dietary saturated fat intake, and exposure to environmental tobacco smoke. The proportion of former smokers was approximately twice as large among case patients (30%) as among control subjects (17%). Pre-existing nonmalignant lung disease was also significantly more frequent among case patients (42%) than among control subjects (36%) *(23),* and case patients consumed more saturated fat than control subjects *(24).* These factors were evaluated formally in the current study with regard to the radon exposure risk, but no appreciable changes in exposure-response patterns were evident.

Radon Levels

The radon levels in the 2664 measured dwellings within Missouri had overall arithmetic and geometric means of 1.6 pCi L^{-1} (59 Bq m^{-3}) and 1.2 pCi L^{-1} (44 Bq m^{-3}), respectively (Table 2). Differences in radon levels between the kitchen and bedroom were slight. The small number of basement readings were about twofold higher than the readings in the normal living space with overall arithmetic and geometric means of 2.8 pCi L^{-1} (104 Bq m^{-3}) and 2.4 PCi L^{-1} (89 Bq m^{-3}), respectively. Winter readings, conducted for a 3-month period, were more than twice as high as year-long readings made in the kitchen and bedroom. The frequency distribution of the 1721 study subjects by TWA residential radon concentrations approximately followed a lognormal distribution (Fig. 1). TWA radon concentrations were exactly the same for case subjects and control subjects (1.82 pCi L^{-1}) as were the median concentrations (1.40 pCi L^{-1}). Slightly more than 6.7% of the study subjects were estimated to be exposed to TWA residential radon levels at or above the EPA action level of 4 pCi L^{-1}. Radon levels greater than 4 PCi L^{-1} were experienced by 6.5% of the case patients and 6.8% of the control subjects.

Year-long track-etch detector readings were made in dwellings occupied by study subjects for 78.4% of the 5- to 30-year period immediately prior to enrollment in the study. (This summary statistic included 78.5% of the period for living case patients, 76.0% for deceased case subjects, and 78.8% for control subjects; these differences were not statistically significant.) Measurements made in the 1273 current homes of case patients and control subjects covered 49.7% of the relevant person-years of radon exposure; the remaining 28.7% person-years came from measurements made in 1391 former houses. Missing person-time of radon coverage occurred for the following reasons: 1) The current dwelling occupant (2%) or landlord (2%) refused to participate in the study; 2) the dwelling was outside Missouri, which made dosimetry prohibitively expensive (8%); 3) the address on the questionnaire was invalid; or 4) the dwelling was destroyed (9%). The amount of time spent outside the home did not vary greatly in this population because relatively few women worked. The overall occupancy factor was quite high, about 84%, and did not differ appreciably between case patients and control subjects. As a result, adjustment for residential occupancy did not alter risk estimates.

Dose-Response Pattern

Twenty percent of the population was exposed to radon concentrations between 2.5 and 15.3 pCi L^{-1} (mean, 4.1 pCi L^{-1}). Compared with the lowest quintile (0.1-0.8 pCi L^{-1}), the relative risk of lung cancer among women exposed to the highest concentrations was 1.20 (95% CI = 0.9-1.7) (Table 3). Compared

Table1. characteristics of women with lung cancer (case subjects) and matched control subjects

Characteristic	Case patients		Control subjects*	
	No.	%	No.	%
Total	538	100.0	1183	100.0
Age, y				
<55	45	8.4	95	8.0
55-64	78	14.5	202	17.1
65-74	166	30.8	384	32.5
75-79	122	22.7	306	25.9
>=80	127	23.6	196	16.6
Mean age, y: 71.0(case); 69.5 (control)				
Education, y				
<12	203	37.8	439	37.1
12	199	37.0	411	34.7
>12	110	20.4	308	26.0
Unknown	26	4.8	25	2.1
Marital stares				
Married	262	48.7	660	55.8
Widowed	228	42.4	439	37.1
Separated	3	0.6	4	0.3
Divorced	25	4.6	44	3.7
Never married	20	3.7	35	3.0
Unknown	0		1	0.1
Interview type				
In-person	197	36.6	1183	100
Next-of-kin	341	63.4	0	0
Smoking history, active				
Never	377	70.1	983	83.1
Former	161	29.9	200	16.9
Cigarette pack-years				
<=l	26	16.1	79	39.5
>1-16.5	43	26.7	74	37.0
>16.5	59	36.6	44	22.0
Unknown	33	20.5	3	1.5
Years stopped				
15-22	67	41.6	65	32.5
23-35	61	37.9	54	27.0
36-54	32	19.9	80	40.0
Unknown	1	0.6	1	0.5
Smoking history, passive				
Cigarette pack-years				
0	250	46.5	551	46.6
>0-15	58	10.8	156	13.2
>15-40	75	13.9	225	19.0
>4O	119	22.1	202	17.1
Unknown	36	6.7	49	4.1
Histologic review				
Adenocarcinoma	262	48.7	N/A	
Other cell types	147	27.3	N/A	
Not reviewed by panel	129	24.0	N/A	
Previous lung disease				
No	311	57.8	752	63.5
Yes	225	41.8	429	36.3
Unknown	2	0.4	2	0.2
Saturated fat, kcal				
Quintile 1(lowest)	65	12.1	187	15.8
Quintile 2	71	13.2	186	15.7
Quintile 3	77	14.3	183	15.5
Quintile 4	73	13.6	186	15.7
Quintile 5 (highest)	106	19.7	184	15.6
Unknown	146	27.1	257	21.7

***N/A =** not applicable.

Table 2. Radon **concentrations** (pCi L^{-1}) in 2664* residences of female lung cancer case patients and control subjects from Missouri according to room and length of radon monitoring

	12-mo measurements			3-mo winter measurements	
	Bedroom	Kitchen	Basement	Bedroom and kitchen	Basement
Arithmetic mean, pCi L^{-1} (SD)	1.63(1.57)	1.59 (1.48)	2.83 (1.70)	3.83 (4.51)	4.98 (3.24)
Geometric mean, pCi L^{-1} (SD)	1.19 (2.23)	1.16(2.23)	2.37 (1.86)	2.49(2.60)	3.92(2.10)
No. of measurements	2797†	2650	17	119	70

*No. of dwellings measured for radon 5-30 years before the enrollment of case patients and control subjects in the study.
†Includes 133 side-by-side quality-control readings.

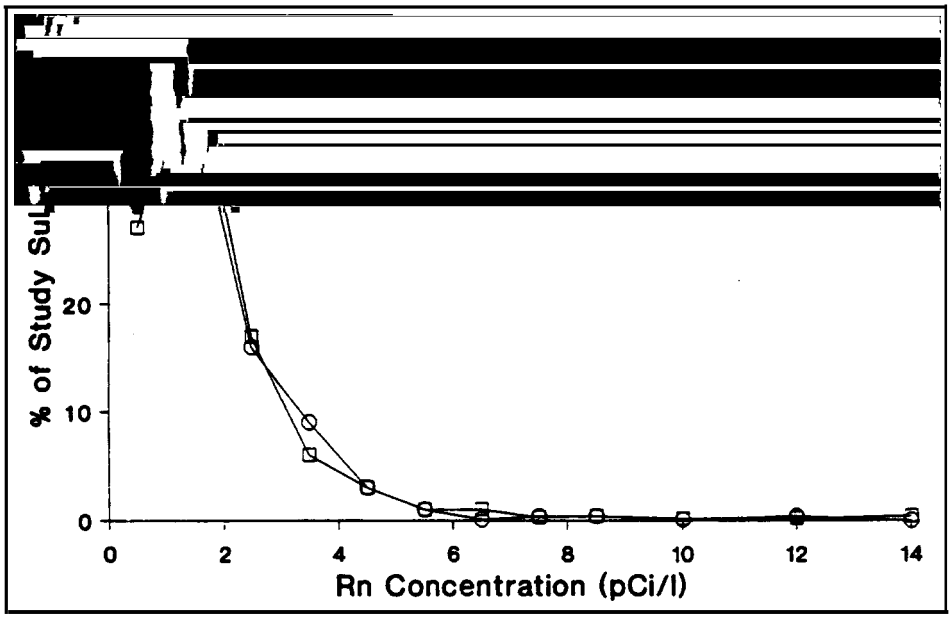

Fig. 1. Distribution of study subjects (and percent distribution) by TWA residential radon concentrations for the 5-to 30-year period prior to study enrollment. Radon measurements were obtained for 78.4% of the relevant residential period. Missing radon concentrations were not imputed.

Table 3. OR for lung cancer by quintiles of TWA residential radon concentration

	TWA radon levels*						P†		
	I	II	III	IV	V	Total	Continuous	Categorical	
Case patients	112	112	93	99	122	538			
Control subjects	233	242	233	252	223	1183			
Total	345	354	326	351	345	1721			
Mean pCi L^{-1}	0.6	1.0	1.4	2.0	4.0				
OR‡	1.00	1.01	0.84	0.90	1.20		.99	.19	
95% CI		0.7-1.4	0.6-1.2	0.6-1.3	0.9-1.7				
			ORs with additional adjustment						***Adjusted for age and:***
	1.00	1.01	0.89	0.88	1.21		.98	.38	Previous smoker
	1.00	0.95	0.83	0.74	1.11		(-).70	.38	Pack-years
	1.00	0.95	0.84	0.77	1.11		(-).72	.38	Pack-years and yearn since smoking cessation
	1.00	1.03	0.89	0.91	1.21		(-).95	.19	Previous lung disease
	1.00	1.01	0.90	0.90	1.24		.95	.17	passive smoking
	1.00	0.97	0.96	0.96	1.43		.30	.03	Amount saturated fat
	1.00	1.01	0.90	0.90	1.24		.92	.14	Education

*The quintile intervals are (I) 0.1-0.79 pCi L^{-1}. (II) 0.80-1.19 pCi L^{-1}. (III) 1.20-1.69 pCi L^{-1}. (IV) 1.70-2.45 pCi L^{-1}, and (V) 2.46-15.3 pCi L^{-1} and are based on the control distribution.

† *P* value for two-sided test of trend. Columns "Continuous" and "Categorical" denote *P* values based on trend test using the actual TWA radon concentrations for individuals (continuous variable) or the mean TWA value of each quintile as the quantitative variable. respectively. Negative sign denotes a decreasing trend with increasing exposure level.

‡ORs adjusted for six categories of age at lung cancer diagnosis for case patients and age at interview for control subjects.

with the lowest decile, however, the relative risk associated with the highest decile was below 1.0. Over quintiles or deciles of radon concentrations, there was no evidence of an increasing lung cancer risk (Fig. 2). Adjustment for lung cancer risk factors had minimal effects on the exposure-response pattern. Trend *P* values were presented on the basis of both actual (continuous) and categorical (grouped) radon values. On the basis of categorical characterizations of radon levels, the *P* values were smaller in all instances. A similar dose-response pattern was observed when a cumulative measure of dose (i.e., WLM) was used in the analysis. Analyses restricted to the 197 case subjects and 1183 control subjects who were living and healthy enough to provide interviews yielded a positive trend of lung cancer risk and residential radon exposure *(P* for linear trend = .06). The ORs for study subjects directly interviewed over the telephone were 1.0, 1.5, 1.3, 1.6, and 1.8 for quintiles of radon concentrations. The use of WLM produced a similar dose-response pattern among study subjects directly interviewed over the telephone. There was no evidence of trend, however, for the 341 case patients for whom a direct interview was not obtainable.

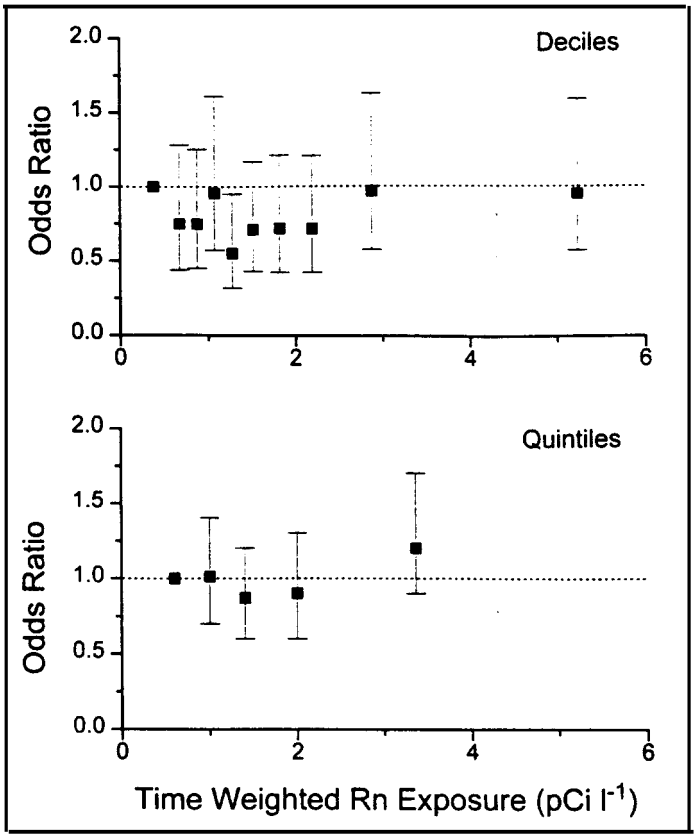

Fig. 2. Age-adjusted ORs for lung cancer by categories of TWA radon concentrations (pCi L^{-1}). Top panel depicts the distribution of lung cancer risk according to deciles of TWA radon concentrations. Bottom panel depicts the distribution of lung cancer risk by quintiles of TWA radon concetrations. Error bars depict 95% confidence intervals on the point estimate of lung cancer risk.

Age and Smoking

The possible modifying effect that age at diagnosis and smoking status might have on radon-related lung cancer risk is shown in Table 4. Age at lung cancer diagnosis was not significantly related to radon risk. Furthermore, the pattern of risk over categories of radon concentration was similar among lifetime nonsmokers and longtime former smokers. In no instance was a statistically significant trend observed.

Histologic Type

The members of the pathology panel were able to histologically review 76% of the 538 lung cancers. For the 262 classified adenocarcinomas, there was suggestive evidence of a dose-response trend, and the OR for the highest quintile of radon concentration was statistically significant (OR = 1.66; 95% CI = 1.0-2.6) (Table 5). When the analysis was adjusted for saturated fat intake, both categorical and continuous trend tests of adenocarcinoma risk and residential radon exposure were significant (P<.05). The use of WLM produced a similar dose-response pattern among case patients with adenocarcinoma. There was no evidence of a dose-response pattern for the other 276 histologically reviewed cell types; the ORs over quintiles of radon concentrations were 1.0, 0.77, 0.74, 0.65, and 0.91. For the histologically confirmed adenocarcinomas, analyses of age and smoking categories were also conducted (not shown in table). There was a hint that those women younger than age 65 at lung cancer diagnosis had a stronger association with indoor radon exposure than older women, but again the *P* value for a

Table 4. OR for all lung cancer by quintiles of TWA residential radon concentration within categories of age and smoking status

	TWA radon levels*					P†		No. of case patients/ control subjects
	I	II	III	IV	V	Continuous	Categorical	
Age group, y								
<65	1.00	0.67	1.33	0.78	1.88	.24	.12	123/297
65-74	1.00	0.81	1.00	0.92	1.10	.95	.48	166/384
2.75	1.00	1.29	0.70	0.93	1.17	(-).56	.61	249/502
Smoking status								
Never smoked	1.00	1.13	0.90	0.91	1.20	(-).99	.38	377/983
Former smoker	1.00	0.80	0.88	0.90	1.32	.95	.24	161/200

*The quintile intervals are defined in Table 3 footnote, ORs were adjusted for six categories of age at interview for control subjects or cancer diagnosis for case patients.

† *P* value for two-sided test of trend. Columns "Continuous" and "Categorical" are defined as in Table 3 footnote(†). Negative sign denotes a decreasing trend with increasing exposure level.

Table 5. OR for the adenocarcinoma tumor type by quintiles of TWA residential radon concentration

	TWA radon levels*						P†	
	I	11	111	Iv	v	Total	Continuous	Categorical
Case patients	41	59	46	53	63	262		
Control subjects	233	242	233	252	223	1183		
Total	272	301	279	305	286	1145		
Median pCi L^{-1}	0.6	1.0	1.4	2.0	3.4			
OR	1.00	1.38	1.06	1.24	1.66			
95% CI		0.9-2.2	0.6-1.8	0.8-2.0	10-2.6			
			OR with additional adjustment					***Adjusted for age and:***
	1.00	1.36	1.07	1.23	1.67		.31	.04 Previous smoker
	1.00	1.24	0.99	1.01	1.51		.50	.09 Pack-years
	1.00	1.25	1.01	1.02	1.52		.51	.01 Pack-years and years since smoking cessation
	1.00	1.39	1.06	1.25	1.66		.32	.05 Previous lung disease
	1.00	1.37	1.05	1.24	1.66		.29	.04 Passive smoking
	1.00	1.17	1.45	1.53	2.06		.04	.01 Saturated fat
	1.00	1.37	1.08	1.24	1.66		.33	.04 Education

*The quintile intervals are as defined in Table 3 footnote (†). ORs were adjusted for six categories of age at interview for control subjects or cancer diagnosis for case patients.

† *P* value for two-sided test of trend. Columns "Continuous" and "Categorical" areas defined in Table 3 footnote.

test for homogeneity was only .80 and not statistically significant. Analyses based on cancer registry diagnoses were essentially the same as those based on the histologically reviewed material.

Discussion

Our large-scale population-based epidemiologic study was one of the first designed specifically to evaluate the association between indoor radon exposure and lung cancer risk. Only recently diagnosed cases of lung cancer were included to minimize the gap between radon measurement and cancer diagnosis and to eliminate potential problems associated with inaccurate death certificate diagnoses. Only lifetime nonsmokers or long-term former smokers were included to minimize the potential confounding of cigarette smoke and to maximize the probability of detecting a radon effect. Year-long radon measurements were sought for all residences lived in by case subjects and control subjects up to 30 years prior to study enrollment, and stringent quality-control procedures were conducted. The amount of time spent indoors (84%) was very high, which suggested that the home measurements might accurately reflect actual radon exposure to lung tissue. Interviews with study subjects or next-of-kin were obtained to control, as necessary, for established lung cancer risk factors. Despite these many study strengths, an association between residential radon and lung cancer risk was not convincingly demonstrated.

There is no question that radon is a human carcinogen. Studies *(20,21)* of underground miners exposed to a broad range of radon concentrations have consistently reported linear dose–response relationships. The reasons for our inability to detect an association between domestic levels of radon and lung cancer may include the following: 1) a limited range of radon concentrations, 2) imprecise estimates of historic radon concentrations. 3) inaccuracy in expected effects based on extrapolations from underground mine exposures, or 4) simply chance. It appears that, while some household exposures to radon are high, the majority of homes in the United States have relatively low levels of exposure. Only 6.7% of our study subjects experienced radon concentrations higher than 4 pCi L^{-1}, and there was no convincing exposure-response pattern overall. Small increases in lung cancer risk associated with these observed levels are difficult to detect by current epidemiologic methods.

The difficulty in accurately estimating radon concentrations that were present many years in the past cannot be overemphasized. We made a concerted effort to measure all homes lived in for the past 30 years, but we were unable to cover 22% of the relevant exposure time. Any inaccuracies in the TWA approach to estimate overall radon exposure and for missing values would dilute any positive relationship with lung cancer *(26)*. No attempt was made to estimate radon concentrations for time periods more than 30 years prior to study enrollment. While the effectiveness of such past radon exposures to cause lung cancer is less than for more recent exposures *(21)*, the contribution to risk is not necessarily negligible and could cloud any exposure-response trend. Furthermore, even with complete coverage of all residences, there is the implicit assumption that a measurement today would reflect accurately exposure conditions of 20-30 years ago. Changes to homes due to structural aging, remodeling, new furnaces, storm windows, and so forth could easily invalidate this assumption. New approaches to measuring radon in former residences, such as radon progeny activity in household glass *(27)*, might prove valuable in the future. Finally, there is the difficulty in making a home measurement and relating it to a lung dose that must take into account the actual time spent in the house as well as physiologic conditions such as breathing rate *(1)*.

While risk estimates from studies of underground miners could not be rejected statistically, there are reasons to believe that they might be overestimates if adjustment is not made for important factors. Arsenic. diesel exhaust, and silica dust, for example. are often found in underground mines and could con-

tribute to cellular proliferation that might enhance the effectiveness of radon to induce cancer *(1)*. These differences in environmental exposures as well as in smoking characteristics might substantially alter the generalizability or representativeness of miner risk estimates to our population. A recent National Research Council meeting concluded that miner estimates should be reduced by up to 30% to account for differences in the home environment *(1)*.

Most studies of miners have included predominantly smoking men, whereas our population was composed entirely of nonsmoking women. Lung cancer excesses have been reported among nonsmoking miners *(28)*, and recent pooled analyses *(20)* of studies of miners indicate a higher risk for nonsmokers than for smokers for the same cumulative exposure, as would be expected if the interaction between radon and tobacco use were somewhat less than multiplicative *(21)*. Thus, our study of nonsmoking women may have been more powerful than originally thought to detect a radon effect.

Overall, there was no evidence of an increasing risk of lung cancer over increasing levels of radon concentrations. However, several subgroup analyses suggested positive dose–response trends, i.e., when analyses were restricted to histologically confirmed adenocarcinomas or to living subjects. Studies *(29)* of underground miners have linked radon exposure to increases in adenocarcinoma, but small-cell cancers are the usual predominant cell type. Similarly, when an association with indoor radon has been suggested for a specific histologic type, it was usually for small-cell carcinomas or non-adenocarcinomas *(8-10)*, and only the national Swedish study *(11)* found a risk for adenocarcinoma. The possibility that adenocarcinomas might be more strongly associated with radon exposure among nonsmoking women than other cell types remains an interesting possibility, but the inconsistency with many other studies leaves open the possibility that the result might be a chance occurrence.

A stronger dose–response trend was observed if analysis were restricted to case patients and control subjects who were living and healthy enough to be interviewed. More accurate information can usually be expected from direct rather than next-of-kin interviews, resulting in less error in exposure measures and stronger dose–response trends. Some recall bias had been suggested, for example, for next-of-kin interviews for some lifestyle factors such as saturated fat consumption and pre-existing lung disease *(23,24)*. It is difficult to imagine, however, how radon misclassification would occur since physical measurements of radon were made in current and previous dwellings occupied by case subjects and control subjects. Residential history conceivably could be inaccurately reconstructed by next-of-kin, but there were no significant differences between the direct and next-of-kin information with regard to mean number of residences or exposure-time coverage. Thus, the analyses based on 197 in-person interviews may indicate either the play of chance in the evaluation of many subsets of the data or some unidentified bias due to inaccurate recall of residential histories by next-of-kin.

Factors other than radon that were associated with lung cancer in these data were also evaluated as potential confounding and effect-modifying factors. No clear patterns were seen with categories of age at diagnosis or smoking status. Adjustment for age and for history of previous lung disease. involuntary cigarette smoke exposure, amount of dietary saturated fat consumed. and educational level had little effect on the overall pattern of lung cancer risk over categories of radon concentration. The *P* values for trend in radon risk varied somewhat depending on the adjustment factor, and adjustment fo, saturated fat intake produced a significant dose–response trend only for adenocarcinoma.

The level of significance of the trend tests was markedly different depending on whether continuous (actual) or categorical (grouped) radon concentrations were analyzed. Analyses based on a continuous exposure variable have the advantage of avoiding the arbitrariness involved in the choice of cut-points. For example, the trend values differed if quintiles or deciles of radon concentrations were analyzed, with deciles yielding less significant results. On the other hand, trend statistics based on categorical means tend to reduce the influence of extreme values. The influence of the choice of trend statistics in the current study points to a lack of robustness in the data being analyzed and suggests a cautious approach to interpreting the results. This instability reflects, perhaps, the small exposure effect to be detected coupled with the uncertainties associated with estimating actual radon exposures so many years in the past.

Our study differs from previous studies of domestic radon exposure by including only nonsmoking subjects. In earlier investigations, cigarette smoking was the most striking cause of lung cancer, with relative risks almost 14-fold for persons smoking more than one pack per day in Stockholm, New Jersey, and Canada and threefold among heavy smokers in China. In the Stockholm study *(10)*, the steepest gradient in risk occurred among those smoking 20 or more cigarettes per day, but there was no comparable dose–response trend for nonsmokers. In the national Swedish study *(11)*, radon-associated risks by smoking status were not significantly different. In New Jersey, an increasing dose-response trend was observed among smokers of fewer than 25 cigarettes per day, no dose-response trend was seen among nonsmokers, and there was a negative dose-response trend in the highest smoking category *(9)*. The Chinese and Canadian data *(8,13)* showed no clear dose–response trend in any smoking category. A recent combined analysis *(14)* of the Stockholm, New Jersey, and Chinese studies concluded that there was a lack of consistency within and across studies for a radon effect overall and within smoking categories. Because the anticipated relative risk from indoor radon is low and less than 1.4 for long-term exposures at 4 pCi L^{-1} [<26 WLM; based on results obtained by the Committee on Biologic Effects of Ionizing Radiation, i.e., BEIR IV, estimates *(21)* from data on underground miners], any inability to control adequately for cigarette smoking might have contributed, in part to these inconsistencies.

Despite convincing evidence that radon causes lung cancer among underground miners, studies of indoor radon have not yet provided a clear picture of the level of risk associated with lifetime low-level exposures. Future efforts to pool similar studies should be encouraged to clarify the potential carcinogenic risk associated with domestic radon exposure.

References

(1) Board on Radiation Effects Research, National Research Council: Comparative Dosimetry of Radon in Mines and Homes. Washington, DC: Natl Acad Press, 1991, pp 9-19

(2) Samet JM: Radon and lung cancer.J Natl Cancer Inst 81:745-757, 1989

(3) Cross FT: A review of experimental animal radon health effects data. In Radiation Research: a Twentieth Century Perspective (Dewey WC, Edington M, Fry RJM, et at, eds). San Diego: Academic Press, 1992, pp 476-481

(4) Abelson PH: Mineral dusts and radon its uranium mines [editorial]. Science 254:777, 1991

(5) Lubin JH, Boice JD Jr: Estimating Rn-induced lung cancer in the United States. Health Phys 57:417-427, 1989

(6) Puskin JS, Nelson CB: EPA's perspective on risks from residential radon exposure. JAPCA 39:915-920, 1989

(7) Stidley CA, Samet JM: A review of ecologic studies of lung cancer and indoor radon [see comment citation in Medline]. Health Phys 65:234-251, 1993

(8) Blot WJ, Xu ZY, Boice JD Jr, et al: Indoor radon and lung cancer its China [see Continent citations in Medline]. J Natl Cancer Inst 82:1025-1030, 1990

(9) Schoenberg JB, Klotz JB, Wilcox HB, et al: case-control study of residential radon and long cancer among New Jersey women. Cancer Res 50:6520-6524, 1990

(10) Pershagen G, Liang ZH. Hrubec Z. et al: Residential radon exposure and lung cancer in Swedish women. Health Phys 63:179-186, 1992

(11) Pershagen G. Akerblom G. Axelson O, et al: Residential radon exposure and lung cancer its Sweden [see comment citations in Medline]. N Engl J Med 330:159-164, 1994

(12) Ruosteenoja E: indoor radon and risk of lung cancer: an epidemiological study in Finland. Ph.D. thesis. STUK-A 99. Helsinki: Finnish Centre for Radiation and Nuclear Safety. 1991

(13) Létourneau EG, Krewski D, Choi NW, et al: A case-control study of residential radon and lung cancer in Winnipeg, Manitoba [see comment citation in Medline]. Am J Epidemiol 140:310-322, 1994

(14) Lubin JH, Liang Z, Hrubec Z, et al: Radon exposure in residences and lung cancer among women: combined analysis of three studies. Cancer Causes Control 5:114-128, 1994

(15) Brownson RC. Davis JR, Chang JC, et al: A study of the accuracy of can-

(16)